

Recurrent copy number variations as risk factors for neurodevelopmental disorders: critical overview and analysis of clinical implications

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ABSTRACT

Neurodevelopmental disorders (NDs) encompass a spectrum of neuropsychiatric manifestations. Chromosomal regions 1q21.1, 3q29, 15q11.2, 15q13.3, 16p11.2, 16p13.1 and 22q11 harbour rare but recurrent CNVs that have been uncovered as being important risk factors for several of these disorders. These rearrangements may underlie a broad phenotypical spectrum, ranging from normal development, to learning problems, intellectual disability (ID), epilepsy and psychiatric diseases, such as autism spectrum disorders (ASDs) and schizophrenia (SZ). The highly increased risk of developing neurodevelopmental phenotypes associated with some of these CNVs makes them an unavoidable element in the clinical context in paediatrics, neurology and psychiatry. However, and although finding these risk *loci* has been the goal of neuropsychiatric genetics for many years, the translation of this recent knowledge into clinical practice has not been trivial. In this article, we will: (1) review the state of the art on recurrent CNVs associated with NDs, namely ASD, ID, epilepsy and SZ; (2) discuss the models used to dissect the underlying neurobiology of disease, (3) discuss how this knowledge can be used in clinical practice.

INTRODUCTION

Neurodevelopmental disorders (NDs) are a large group of clinical entities encompassing a spectrum of neuropsychiatric manifestations caused by disruption of brain development, including autism spectrum disorders (ASD), intellectual disability (ID), communication disorders, attention deficit and hyperactivity disorder (ADHD), specific learning disorders and motor disorders.¹ Schizophrenia (SZ) has also been proposed to result from neurodevelopmental disturbances, usually manifesting only in the adult stage.² The majority of NDs do not fit the Mendelian disease model where one gene is responsible for a given trait.³ Most of them are polygenic or multifactorial and their clustering in families is believed to be influenced by genetic and environmental factors.⁴

Two contrasting hypotheses have been advanced to explain the nature of this complexity: the common variant common disease (CVCD) and the rare variant common disease (RVCD) models.⁵ According to the CVCD model, the genetic risk in an individual is attributable to many high frequency variants, each one having a modest effect on risk. In contrast, the RVCD model states that genetic risk in a given individual can be explained by rare mutations that confer significant risk.^{5,6}

Most likely, both types of contribution are important; the narrow-sense heritability in autism is ~52.4%, most being due to common variants.⁷ Rare CNVs—DNA segments larger than 1 Kb that present a copy number different from that of the reference genome⁸—contribute to a substantial proportion of the genetic variability in humans⁹ but can also contribute for risk of developing a neurodevelopmental disturbance. Its association with a range of NDs^{5,10} was only possible because advancements in chromosomal microarray (CMA) technology have allowed for CNV analysis in very large case-control cohorts.¹¹

A significant proportion of risk for ID, ASD, SZ, epilepsy, bipolar disease (BD) and ADHD can be explained by these rare variants.^{12–20} The estimated risk, or OR, for most common disease-associated single nucleotide polymorphisms will be of—at most—up to 2 (with many between 1.1 and 1.4); in contrast, many—if not most—rare variants have been associated with ORs greater than 2, in some cases considerably larger.⁶

Most of the experiments to study the impact of CNVs in dosage-sensitive gene expression in normal brain development have used lymphoblastoid cell lines, suggesting a functional impact of CNVs via transcriptome alterations.^{21–23} Two studies on postmortem brain samples have shown that 1q21.1 and 22q11.2 CNVs influence gene expression in the dorsolateral prefrontal cortex;^{24,25} interestingly, a significant proportion of CNVs influencing gene expression in the human prefrontal cortex were located in chromosomal regions implicated in psychiatric disorders, namely those in 1q21.1, 3q29, 15q11.2, 16p11.2, 16p13.1, 17q12 and 22q11.2.²⁵

Most recurrent pathogenic CNVs are large (>400 kb), typically involving dozens of genes, and are individually rare (frequency <0.1%).¹¹ Their discovery emphasised the importance of de novo and essentially private mutations in NDs, and indicated that the distinction between milder neuropsychiatric conditions and severe developmental impairment may be a consequence of increased mutational burden affecting multiple genes in the latter case.³

Although finding such risk *loci* has been the goal of neuropsychiatric genetics for many years, the translation of this recent knowledge into clinical practice has not been trivial. In this article, we will: (1) review the state of the art on recurrent CNVs associated with NDs, namely ASD, ID, epilepsy and SZ; (2) discuss the models used to dissect the underlying mechanism of disease, (3) discuss how this knowledge can be used in clinical practice.

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RECURRENT CNVs ASSOCIATED WITH INCREASED RISK FOR NDS

The chromosomal regions 1q21.1, 3q29, 15q11.2, 15q13.3, 16p11.2, 16p13.1 and 22q11 harbour some of the rare recurrent CNVs that have been uncovered as being risk factors for several NDs. Some of these studies are summarised in tables 1–8 and their main aspects discussed below. Other CNVs associated with risk of NDs are listed in table 9.

1q21.1 rearrangements

The distal 1q21.1 region includes 30 genes and is flanked by segmental duplications that mediate recurrent rearrangements with conserved break points (BP). Recurrent 1.35 Mb deletions/duplications occur between BP3 and BP4 (figure 1) and confer a risk for a variety of phenotypes (table 1): the deletions are mainly associated with ID and epilepsy, being also enriched in SZ or schizoaffective disorders,^{26–31} while the duplications are associated with ID and ASD; other findings include seizures, microcephaly/macrocephaly, mild dysmorphisms and congenital abnormalities (CAs).⁵⁸

Of note, there seems to exist a mirror effect on head circumference: deletions cause microcephaly and duplications cause macrocephaly.⁵⁹ These differences might be partially explained by the variable dosage of genes contained in the CNV region. The 1q21.1 *HYDIN* paralog, which is dosage sensitive and exclusively expressed in the brain, appears to be important in determining head size: an atypical deletion that did not include this gene was observed in a normocephalic patient.⁵⁹ *PRKAB2*, which encodes the protein kinase, AMP-activated, β -2 non-catalytic subunit, has effects only when deleted;⁶⁰ this finding is in agreement with previous studies that have demonstrated profound abnormalities in the central nervous system (CNS) in AMP-activated protein kinase (AMPK)-b1–/– knockout mice.⁶¹

3q29 rearrangements

The 3q29 microdeletion (3q29del) is particularly rare (<1/1000) and was first described in patients with mild-to-moderate ID and slightly dysmorphic facial features.⁶³ Since then, other works have associated this deletion with ID, developmental delay (DD), BD, learning disability, CAs^{12 27} and especially with SZ.^{30–32} The reciprocal microduplication is associated with mild-to-moderate ID and CAs (table 2).^{12 27 63}

3q29del encompasses 21 genes (figure 2), including *DLG1*, *PAK2* and *FBXO45*, that are related to neuronal postsynaptic membrane function and *PTEN* signalling, and have been proposed as determinant for the psychiatric manifestations of patients harbouring these deletions.⁶⁴ Recently, rare single nucleotide variants as well as small insertions and deletions in *FBXO45* were identified in patients with SZ.⁶⁵

15q11.2 (BP1-BP2) deletions

The 15q11.2 (BP1-BP2) microdeletions (15q11.2del) range from 253 Kb to 1.5 Mb and have been associated with ID, SZ, DD and ASD, as well as with epilepsy (table 3).^{33 36 38} In fact, the combined frequency of this CNV along with 15q13.3del and 16p13.11del is approximately 3% in patients with genetic generalised epilepsy (GGE),⁶⁶ and these CNVs are particularly enriched in patients with ID plus GGE when compared with individuals with GGE or ID alone.^{14 67}

In spite of its location in the Prader-Willi/Angelman syndrome region, it does not contain the critical genes for these syndromes. This CNV encompasses four non-imprinted genes (figure 3): *NIPA1*, *NIPA2*, *CYFIP1* and *TUBGCP5*.^{36 38} Three of them are implicated in CNS development and/or function: *NIPA1* and *NIPA2* are widely expressed in neuronal tissues and CNS and mediate magnesium (Mg^{2+}) transport;^{68 69} when mutated, they cause autosomal dominant hereditary spastic paraplegia⁷⁰ and childhood absence epilepsy,⁷¹ respectively. *CYFIP1* is expressed

Table 1 Studies describing association of 1q21.1 deletions and duplications with several NDs

References	Phenotype	del/dup	Case group			Control group			p Value	OR
			N	CNVs, n	Frequency (%)	N	CNVs, n	Frequency (%)		
26	ID/DD/ASD	del	5218	25	0.48	4737	0	0	1.1×10^{-7}	>22.8
27	ID/DD/ASD/CAs	del	15 749	55	0.35	10 118	3	0.03	5.4×10^{-9}	12
12	ID/DD/CAs	del	15 767	47	0.30	8329	2	0.024	3.3×10^{-7}	12
28	SZ/RP	del	4718	11	0.23	41 199	8	0.019	$2.9 \times 10^{-5*}$	12
29†	SZ	del	7918	17	0.21	46 502	11	0.024	2.5×10^{-8}	9.1
						14 060‡	3‡	0.021‡	$9.6 \times 10^{-6‡}$	10‡
30	SZ	del	3945	4	0.10	3611	1	0.028	$2.2 \times 10^{-8}\S$	3.7
			11 392§	20§	0.18§	47 321§	10§	0.021§		8.3§
31	SZ	del	6882	12	0.17 0.17§	6316	1	0.016 0.021§	2.7×10^{-3}	11
			19 056§	33§		81 829 §	17§		$4.1 \times 10^{-13}\S$	8.35§
26	ID/DD/ASD	dup	5218	9	0.17	4737	1	0.021	2×10^{-2}	8.2
27	ID/DD/ASD/CAs	dup	15 749	28	0.18	10 118	3	0.03	4×10^{-4}	6
12	ID/DD/CAs	dup	15 767	25	0.16	8329	6	0.07	2×10^{-4}	2.2
30	SZ	dup	3945	7	0.18	3611	0	0	$2 \times 10^{-3‡}$	6.4
			8563‡	11‡	0.13‡	39 809‡	14‡	0.035‡		3.7‡
31	SZ	dup	6882	8	0.12 0.13 ^d	6316	5	0.079 0.037 ^d	3.5×10^{-1}	1.47
			16 247§	21 ^d		64 046 ^d	24 ^d		9.9×10^{-5d}	3.45 ^d

p Value: Fisher's exact test, unless specified.

*Cochran-Mantel-Haenszel test.

†Data obtained from current and previous studies.

‡Without Icelandic controls.

§Meta-analysis values, combined data from previous studies and current data set.

ASD, autism spectrum disorder; CA, congenital anomaly (including cardiac, cataract and microcephaly); DD, developmental delay; ID, intellectual disability; ND, neurodevelopmental disorder; SZ/RP, schizophrenia/related psychosis.

Table 2 Studies describing association of 3q29 deletions and duplications with SZ, schizoaffective disorders and other NDs

References	Phenotype	del/dup	Case group			Control group			p Value	OR
			N	CNVs, n	Frequency (%)	N	CNVs, n	Frequency (%)		
32	SZ	del	245 7545*	1 6*	0.41 0.08*	490 39 748*	0 1*	0 0.0025*	9.7×10 ⁻³ *†	32* 17*†
30	SZ	del	3945 7336*	5 7*	0.13 0.096*	3611 14 821*	0 0*	0 0*	4×10 ⁻² 4×10 ⁻⁴ *	>4.6 >14*
31	SZ	del	6882 17 005*	4 14*	0.058 0.082*	6316 69 965*	0 1*	0 0.0014*	7.4×10 ⁻² 1.5×10 ⁻⁹ *	>3.7 57.65*
27	ID/DD/ASD/CAs	del	15 749	9	0.057	10 118	0	0	1.47×10 ⁻²	>5.8
12	ID/DD/CAs	del	15 767	6	0.038	8329	0	0	7.85×10 ⁻²	>3.2
27	ID/DD/ASD/CAs	dup	15 749	8	0.050	10 118	1	0.0099	1×10 ⁻¹	5.14
12	ID/DD/CAs	dup	15 767	4	0.025	8329	0	0	1.83×10 ⁻¹	>2.1

p Value: Fisher's exact test, unless specified.

*Meta-analysis values, combined data from previous studies and current data set.

†Cochran-Mantel-Haenszel test.

ASD, autism spectrum disorder; CAs, congenital anomaly (including cardiac, cataract and microcephaly); DD, developmental delay; ID, intellectual disability; ND, neurodevelopmental disorder; SZ: schizophrenia.

in the brain and encodes a protein that interacts with fragile X mental retardation protein (FMRP), the protein product of the fragile X syndrome gene.⁷² FMRP and CYFIP1 play an important role in the regulation of mRNAs in brain,⁷³ and *CYFIP1* is critical for the maintenance of dendritic complexity and the stabilisation of mature spines; dysregulation of *CYFIP1* expression levels leads to pathological changes in CNS maturation and neuronal connectivity, which may contribute to the development of neuropsychiatric illness.⁷⁴ Finally, *TUBGCP5* encodes a widely expressed core component of the gamma tubulin complex, required for microtubule nucleation at the centrosome.⁷⁵

15q13.3 (BP4-BP5) rearrangements

Sharp and colleagues first described patients with ID, epilepsy and variable facial and digital dysmorphisms due to a 1.5-Mb deletion at 15q13.3 (15q13.3del), comprising the BP4-BP5 region (figure 3).⁷⁶ Patients with reciprocal duplications and a patient with a homozygous deletion and a severe phenotype including epileptic encephalopathy and autistic features were also observed.^{77 78} This deletion is strongly associated with ID (OR >29.6)²⁷ and with SZ and related psychoses,^{28–31} while the reciprocal duplications seem to predispose to ADHD (table 4).²⁰ The 15q13.3del was also recognised as a

Table 3 Studies describing association of BP1-BP2 15q11.2 deletions with several NDs

References	Phenotype	del/dup	Case group			Control group			p Value	OR
			N	CNVs, n	Frequency (%)	N	CNVs, n	Frequency (%)		
28	SZ/RP	del BP1-BP2	4718	26	0.55	41 194	79	0.19	6×10 ⁻⁴ *	2.9 2.73*
29†	SZ	del BP1-BP2	7918	49	0.62	46 497 14 055†	103 45†	0.22 0.32†	4.46×10 ⁻⁸ 1.7×10 ⁻³ ‡	2.8 1.94‡
31	SZ	del BP1-BP2	6882 19 547§	44 116§	0.64 0.59§	6316 81 802§	26 227§	0.41 0.28§	4.6×10 ⁻² 2.5×10 ⁻¹⁰ §	1.56 2.15§
33	I GE	del BP1-BP2	1234	12	0.97	3022	6	0.20	4.2×10 ⁻⁴	4.9
34	Unexplained ID	del BP1-BP2	1010	8	0.79	2493	3	0.12	3×10 ⁻³	6.6
12	ID/DD/CAs	del BP1-BP2	15 767	94	0.6	8329	19	0.23	2.1×10 ⁻⁵	2.6
35	DD/ID/ASD	del BP1-BP2	25 113	203	0.81	22 246	84	0.38	<1×10 ⁻⁴	2.15
36	DD/ASD ADD/ADHD	del BP1-BP2	17 000	69	0.41	6329	16	0.25	8.7×10 ⁻²	1.6
37	ASD	del BP1-BP2	1257	4	0.32	1577	4	0.25	7.4×10 ⁻¹	1.26
38	ASD ASD¶	del BP1-BP2	636 448¶	7 6¶	1.1 1.3¶	1603	12	0.75	4.2×10 ⁻¹ 2.5×10 ⁻¹ ¶	1.47 1.79¶

p Value: Fisher's exact test, unless specified.

*Cochran-Mantel-Haenszel test.

†Data obtained from current and previous studies.

‡Without Icelandic controls.

§Meta-analysis values, combined data from previous studies and current data set.

¶ASD with normal intelligence.

ADD/ADHD, attention deficit/attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BP, break point; CA, congenital anomaly; DD, developmental delay; ID, intellectual disability; IGE, idiopathic generalised epilepsies; ND, neurodevelopmental disorder; SZ/RP, schizophrenia/related psychosis.

Table 4 Studies describing association of 15q13.3 Bp4-BP5 deletions and duplications with several NDs

References	Phenotype	del/dup	Case group			Control group			p Value	OR
			N	CNVs, n	Frequency (%)	N	CNVs, n	Frequency (%)		
³⁹	IGE	del BP4-BP5	1223	12	0.99	3699	0	0	5.3×10^{-8}	>36.6
⁴⁰	IGE	del BP4-BP5	539	7	1.3	3777	0	0	4.6×10^{-7}	>49.7
²⁷	ID/DD/ASD/CAs	del BP4-BP5	15 749	46	0.29	10 118	0	0	1.44×10^{-10}	>29.6
¹²	ID/DD/CAs	del BP4-BP5	15 767	42	0.27	8329	0	0	1.8×10^{-8}	>22
²⁸	SZ/RP	del BP4-BP5	4213	7	0.17	39 800	8	0.02	$5.3 \times 10^{-4*}$	8.3 11.54*
^{29†}	SZ	del BP4-BP5	7413	15	0.20	45 103 12 661‡	8 1‡	0.018 0.008‡	2.8×10^{-8} $3.34 \times 10^{-6}‡$	11.4 25.7‡
³⁰	SZ	del BP4-BP5	3945 10 887§	7 21§	0.18 0.19§	3611 45 922§	1 9§	0.028 0.018§	$2.0 \times 10^{-9}§$ $0.018§$	6.4 9.9§
³¹	SZ	del BP4-BP5	6882 18 571§	4 26§	0.058 0.14§	6316 80 422§	2 15§	0.032 0.019§	3.8×10^{-1} $4.0 \times 10^{-10}§$	1.84 7.52§
²⁰	ADHD	dup BP4-BP5	3003	37	1.25	10 620	64	0.61	1.78×10^{-4}	2
²⁷	ID/DD/ASD/CAs	dup BP4-BP5	15 749	14	0.089	10 118	3	0.03	8.3×10^{-2}	3
¹²	ID/DD/CAs	dup BP4-BP5	15 767	20	0.12	8329	3	0.036	2×10^{-2}	3.5

p Value: Fisher's exact test, unless specified.

*Cochran-Mantel-Haenszel test.

†Data obtained from current and previous studies.

‡Without Icelandic controls.

§Meta-analysis values, combined data from previous studies and current data set.

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BP, break point; CA, congenital anomaly (including cardiac, cataract and microcephaly); DD, developmental delay; ID, intellectual disability; IGE, idiopathic generalised epilepsy; ND, neurodevelopmental disorder; SZ/RP, schizophrenia/related psychosis.

major risk factor (OR >50) for idiopathic generalised epilepsies (IGE).³⁹ In addition to this variable expressivity, incomplete penetrance (ie, healthy individuals presenting these deletions) has been observed,^{33 40} probably due to additional

genetic abnormalities, epigenetic factors and/or modifier genes and CNVs.⁷⁹

The critical region of 15q13.3del harbours at least seven genes (*ARHGAP11B*, *FAN1/MTMR15*, *MTMR10*, *TRPM1*,

Table 5 Studies describing association of proximal 16p11.2 deletions and duplications with ASD, SZ and other NDs

References	Phenotype	del/dup	Case group			Control group			p Value	OR
			N	CNVs, n	Frequency (%)	N	CNVs, n	Frequency (%)		
⁴¹	ASD	proximal del	712	4	0.56	837	0	0	4.4×10^{-2}	>4.7
⁴²	ASD	proximal del	2195	8	0.37	2519	4	0.16	2.5×10^{-1}	2.3
²⁷	ID/DD/ASD/CAs	proximal del	15 749	67	0.43	10 118	5	0.049	6.3×10^{-10}	8.4
¹²	ID/DD/CAs	proximal del	15 767	64	0.41	8329	3	0.037	3.4×10^{-9}	11.3
³⁰	SZ	proximal del	3945 9890*	1 4*	0.025 0.04*	3611 29 597*	3 11*	0.08 0.037*	$5.4 \times 10^{-1*}$	0.91 1.09*
³⁰	SZ	proximal dup	3945 9890*	13 31*	0.33 0.31*	3611 29 597*	1 8*	0.028 0.027*	$1.5 \times 10^{-12*}$	11.9 11.6*
³¹	SZ	proximal dup	6882 16 772*	27 58*	0.39 0.35*	6316 63 068*	0 19*	0.03* 0.03*	2.3×10^{-8} $2.9 \times 10^{-24*}$	>24.9 11.5*
⁴²	ASD	proximal dup	2195	9	0.41	2519	4	0.16	1.6×10^{-1}	2.6
²⁷	ID/DD/ASD/CAs	proximal dup	15 749	39	0.25	10 118	4	0.098	2.5×10^{-5}	6.28
¹²	ID/DD/CAs	proximal dup	15 767	28	0.18	8329	2	0.024	4×10^{-4}	7.4

p Value: Fisher's exact test, unless specified.

*Meta-analysis values, combined data from previous studies and current data set.

ASD, autism spectrum disorder; CAs, congenital anomaly (including cardiac, cataract and microcephaly); DD, developmental delay; ID, intellectual disability; ND, neurodevelopmental disorder; SZ, schizophrenia.

Table 6 Studies describing association of distal 16p11.2 deletions and duplications with ASD, SZ and other NDs

References	Phenotype	del/dup	Case group			Control group			p Value	OR
			N	CNVs, n	Frequency (%)	N	CNVs, n	Frequency (%)		
⁴³	SZ	distal del	13 850	13	0.094	19 954	3	0.015	1×10^{-3}	6.25
³¹	SZ	distal del	6882	0	0	6316	2	0.032	1	–
			20 732*	13*	0.063*	27 045*	5*	0.018*	1.7×10^{-2} *	3.39*
¹²	ID/DD/CAs	distal del	15 767	15	0.095	8329	1	0.024	1.1×10^{-2}	7.9
⁴⁴	DD	distal del	23 084	31	0.13	7700	1	0.013	3×10^{-3}	10.4
¹²	ID/DD/CAs	distal dup	15 767	14	0.089	8329	2	0.012	4.9×10^{-2}	3.7
⁴⁴	DD	distal dup	23 084	17	0.07	7700	3	0.04	4×10^{-1}	1.9

p Value: Fisher's exact test, unless specified.

*Meta-analysis values, combined data from previous studies and current data set.

ASD, autism spectrum disorder; CA, congenital anomaly (including cardiac, cataract and microcephaly); DD, developmental delay; ID, intellectual disability; ND, Neurodevelopmental disorder; SZ, schizophrenia.

KLF13, *OTUD7A* and *CHRNA7*), but *CHRNA7* soon emerged as a prime candidate gene responsible for some of the clinical findings associated with these CNVs, such as seizures, because of the identification of individuals with deletions containing only this gene.⁸⁰ *CHRNA7* encodes the cholinergic receptor alpha 7 (neuronal), which belongs to the nicotinic acetylcholine receptor (nAChRs) superfamily of ligand-gated ion channels that mediate signal transmission at synapses. It plays roles in central and peripheral nervous system development, cognitive performance and inflammation;⁸¹ it is highly expressed in the reticular thalamus, indicating a role in modulating thalamocortical pathways, which are central to the generation of primary generalised seizures seen in IGE. Indirect evidence for its role in epileptogenesis comes from the fact that mutations in other nAChR family members cause autosomal dominant nocturnal frontal lobe epilepsy.^{39 40} Nevertheless, no patients with point mutations in *CHRNA7* gene were described until now:^{62 82} only some non-coding variants associated with reduced gene

expression have been found in one patient with ASD⁸³ as well as in patients with SZ.⁸¹ The $\alpha 7$ nAChR is also a relevant pharmacological target, as agonists of nAChRs are currently being considered in the treatment of NDs.^{84–86} In a maternal immune activation (MIA) mouse model, a murine model of environmental risk factors for autism and SZ, it was shown that this receptor modulates the inflammatory response after MIA, affecting the fetal brain development and offspring behaviour. The $\alpha 7$ nAChR suppresses inflammatory response in the fetal brain by inhibiting interleukin (IL) 6 production and, consequently, the loss of *Chrna7* in the offspring increases their vulnerability to MIA-induced autistic and SZ-like symptoms. Maternal choline supplementation triggers an anti-inflammatory response in the fetal brain and thus decreases the MIA-induced IL-6 elevation during embryonic stage and the autistic and SZ-like behaviours in the adults.⁸⁷

Whole-exome sequencing (WES) data combined with a statistical method designed to identify the responsible gene(s) within

Table 7 Studies describing association of 16p13.11 deletions and duplications with several NDs

References	Phenotype	del/dup	Case group			Control group			p Value	OR
			N	CNVs, n	Frequency (%)	N	CNVs, n	Frequency (%)		
⁴⁵	ID/CAs	del	1027	5	0.49	2014*	0	0	4.8×10^{-3}	>9.85
²⁷	ID/DD/ASD/CAs	del	15 749	22	0.14	10 118	3	0.03	6.3×10^{-3}	4.7
¹²	ID/DD/CAs	del	15 767	18	0.11	8329	3	0.036	3.6×10^{-2}	3.2
⁴⁶	SZ	del	4345	5	0.12	35 079	15	0.04	$>5 \times 10^{-2}$	2.7
³³	IGE	del	1234	6	0.49	3022	2	0.066	9×10^{-3}	7.4
⁴⁷	ES	del	3812	23	0.60	1299	0	0	NA	>7.88
⁴⁵	ID/CAs	dup	1027	7	0.68	2014*	5	0.25	1.27×10^{-1}	2.8
²⁷	ID/DD/ASD/CAs	dup	15 749	45	0.29	10 118	20	0.2	2×10^{-1}	1.4
¹²	ID/DD/CAs	dup	15 767	24	0.15	8329	10	0.12	3.3×10^{-1}	1.3
⁴⁸	ADHD	dup	366	6	1.67	1047	1	0.096	8×10^{-4}	17.4
			825†	4†	0.49†	35 243†	36†	0.1†	3.1×10^{-2} †	4.76†
⁴⁶	SZ	dup	4345	13	0.30	35 079	32	0.09	7×10^{-3}	3.3
³¹	SZ	dup	6882	24	0.35	6316	12	0.19	5.6×10^{-2}	1.84
			12 029‡	37‡	0.31‡	69 289‡	93‡		5.7×10^{-5} ‡	2.30‡

p Value: Fisher's exact test, unless specified.

*Used their own controls with already described data.

†Replication Icelandic group.

‡Meta-analysis values, combined data from previous studies and current data set.

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CA, congenital anomaly (including cardiac, cataract and microcephaly); DD, developmental delay; ES, epilepsy syndrome; ID, intellectual disability; IGE, idiopathic generalised epilepsy; NA, not available; ND, neurodevelopmental disorder; SZ, schizophrenia.

Table 8 Studies describing association of 22q11.2 deletions and duplications with SZ and other NDs

References	Phenotype	del/dup	Case group			Control group			p Value	OR
			N	CNVs, n	Frequency (%)	N	CNVs, n	Frequency (%)		
32	SZ	del	245 6107*	2 29*	0.82 0.48*	490 6502*	0 0*	0 0*	4.7×10 ⁻¹⁰ *†	>31*
30	SZ	del	3945 11 400*	21 35*	0.54 0.31*	3611 45 361*	0 0*	0 0*	<1.0×10 ⁻¹⁶ *	>19 >139*
31	SZ	del	6882 19 084*	20 56*	0.29 0.29*	6316 77 055*	0 0*	0 0*	2.2×10 ⁻⁶ 4.4×10 ⁻⁴⁰ *	>18 >226*
27	ID/DD/ASD/CAs	del	15 749	93	0.59	10 118	0	0	9.1×10 ⁻²¹	>60
12	ID/DD/CAs	del	15 767	96	0.61	8329	0	0	<1×10 ⁻⁴	>51
42	ASD	dup	2195	9	0.41	2519	0	0	1×10 ⁻³	>10
27	ID/DD/ASD/CAs	dup	15 749	32	0.20	10 118	5	0.049	1.1×10 ⁻³	4.1
12	ID/DD/CAs	dup	15 767	50	0.32	8329	5	0.06	1.3×10 ⁻⁵	5.3

p Value: Fisher's exact test, unless specified.

*Meta-analysis values, combined data from previous studies and current data set.

†Cochran-Mantel-Haenszel test.

ASD, autism spectrum disorder; CAs, congenital anomaly (including cardiac, cataract and microcephaly); DD, developmental delay; ID, intellectual disability; ND, neurodevelopmental disorder; SZ, schizophrenia.

regions affected by de novo CNVs, allowed the discovery of a new gene containing rare risk variants for SZ and ASD located in 15q13.3. Fanconi-associated nuclease 1 (*FAN1*) is relatively widely expressed in brain and encodes a DNA repair enzyme.⁸⁸ Individuals carrying a homozygous microdeletion spanning *FAN1* show severe neurodevelopmental abnormalities, including microcephaly.⁸⁹ It is likely that deleterious *FAN1* mutations increase risk for SZ and ASD by interfering with aspects of early neuronal development, namely proliferation.⁸⁸

16p11.2 rearrangements

The 593-Kb proximal deletions and duplications at 16p11.2 (figure 4), although observed in individuals with normal phenotypes,⁹⁰ have been associated with a broad range of NDs (table 5). A detailed phenotypical analysis of the 16p11.2 CNV

has shown the existence of partially mirroring phenotypes: the deletion is associated with ASD, ID, behavioural disorders, CAs, diabetes-independent obesity and macrocephaly, while the reciprocal duplication is associated with autism and SZ, anorexia and microcephaly.^{41 91–95} Jacquemont and colleagues have thus speculated that head circumference and neuronal circuitry abnormalities could be linked to cognitive function and energy balance impairments in patients with 16p11.2 rearrangements, and so the abnormal food intake could be a direct result of a particular ND.⁹⁵ Conceptually, this would make us add obesity to the list of CNV-associated NDs, an intriguing shift to the field, but one that fits the increasing knowledge on the biology of food intake and metabolism regulation by the CNS.⁹⁶

KCTD13 is one of the 29 annotated genes within this CNV, among some transcription factors (eg, *MAZ*, *TBX6*), chromatin

Table 9 Selected studies describing association of other risk loci with NDs

Gene	Associated CNV	Location	Phenotype	References
<i>NRXN1</i>	del	2p16.3	ASD/SZ	31 49–52
<i>CNTN4</i>	del/dup	3p26	ASD	53 54
<i>UBE3A</i> ; <i>PARK2</i> ; <i>RFWD2</i> ; <i>FBXO40</i> ; <i>NLGN1</i> ; <i>ASTN2</i>	del/dup within or surrounding genes	15q11.2/6q25.2–q27 1q25.1–q25.2/3q13.33 3q26.31/9q33.1	ASD	42
<i>SHANK2</i> ; <i>SYNGAP1</i> ; <i>DDX53-PTCHD1</i> <i>DLGAP2</i>	Del dup	11q13.3/6p21.32/Xp22.1 8p23.3	ASD	16
<i>SHANK1</i> ; <i>SHANK2</i> ; <i>SHANK3</i>	del/dup, truncating mutations	19q13.3/11q13.3/22q13.3	ASD/ID/SZ/ ADHD/BD	55
WBS region (38 genes)	dup	7q11.23	ASD/SZ	18 31 56 57
<i>USP7</i> ; <i>C16orf72</i> ; <i>CDH13</i>	dup del	16p13.2 16q23.3	ASD	18
<i>COMMD1</i> ; <i>CACNA2D4</i> ; <i>CTNNA3</i> ; <i>CTNND2</i>	del	2p15/12p13.33 10q22.2/5p15.2	ASD	17
<i>JAKMIP1</i> ; <i>NLGN4Y</i> ; <i>OXTR</i> ; <i>ABAT</i>	del	4p16.1/Yq11.221 3p25/16p13.2	ASD	50
<i>DRG1</i> ; <i>GJA1</i> ; <i>EPHA5</i> ; <i>SPOCK3</i>	dup del	10q11.23/6q22.31/4q13.1 4q32.3	ASD	10
<i>FMO</i> ; <i>DNM</i> ; <i>SATB2</i> ; <i>PEX13</i> to <i>AHSA2</i> ; <i>JAGN1</i> to <i>TATDN2</i> ; <i>CHMP2B</i> to <i>POU1F1</i> ; <i>GAP43</i> ; <i>FGF12</i> ; <i>BMP3</i> ; <i>MEF2C</i> ; <i>SFTPD</i> to <i>GLUD1</i> , including <i>NRG3</i> ; <i>SCNN1A</i> to <i>PIANP</i>	del/dup	1q24/2q33.1/2p15-16.1/3p25.3/3p11.2/ 3q13/3q28–29/4q21/5q14/9p13/10q11/ 10q23.1/12p13	DD	52

ADHD, attention deficit and hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disease; DD, developmental delay; ID, intellectual disability; ND, neurodevelopmental disorder; SZ, schizophrenia.

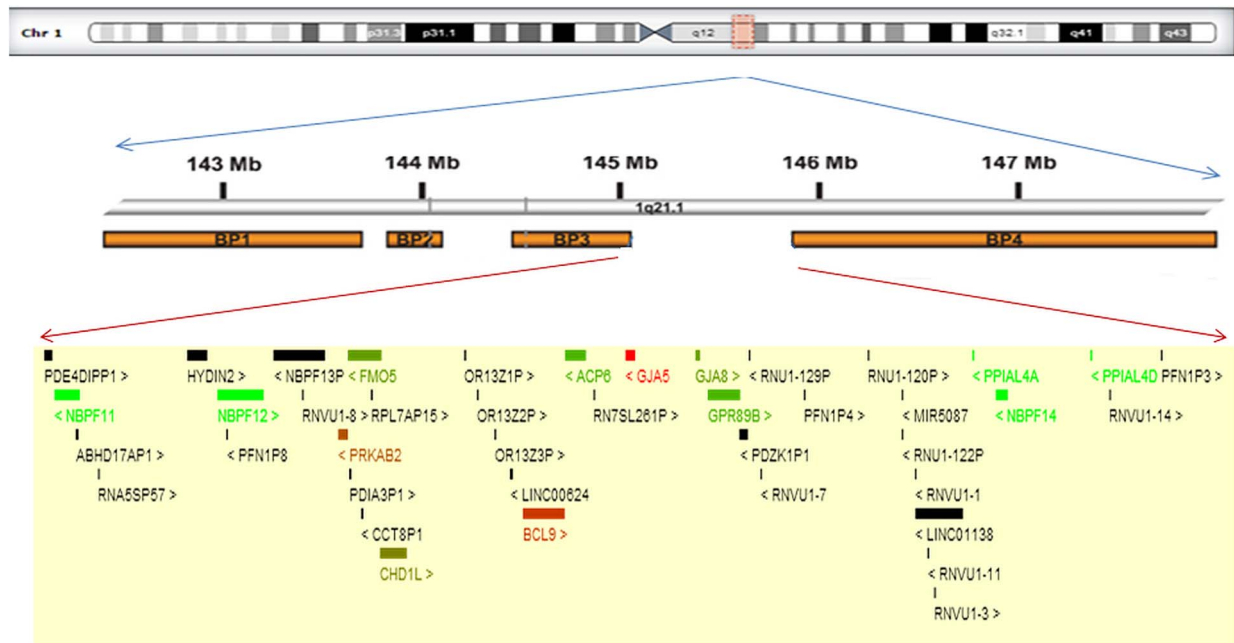


Figure 1 Distal 1q21.1 CNVs: recurrent 1.35 Mb deletions/duplications between break points BP3 and BP4 (chr1: 146.5–147.9 Mb). Protein-coding genes are marked in colour, the remaining are marked in black. Within protein-coding, genes have been scored according to their predicted probability of exhibiting haploinsufficiency: in red are the genes more likely to exhibit haploinsufficiency, in green the genes less likely to exhibit haploinsufficiency (adapted from Firth and colleagues¹⁶¹).

modifiers (eg, *HIRIP3*, *INO80E*) and other genes with a wide array of cellular functions. The use of zebra fish and mouse models revealed that *KCTD13* is a major driver of the head size phenotypes associated with the 16p11.2-CNVR through the regulation of early neurogenesis. Moreover, *KCTD13* dosage

changes were related with autism in a family with a reduced 16p11.2 deletion (encompassing only five genes, one of them being *KCTD13*), and a patient with a narrow diagnosis of autism and a complex 16p11.2 rearrangement involving de novo structural alteration of *KCTD13*.⁹⁷ RNA sequencing of

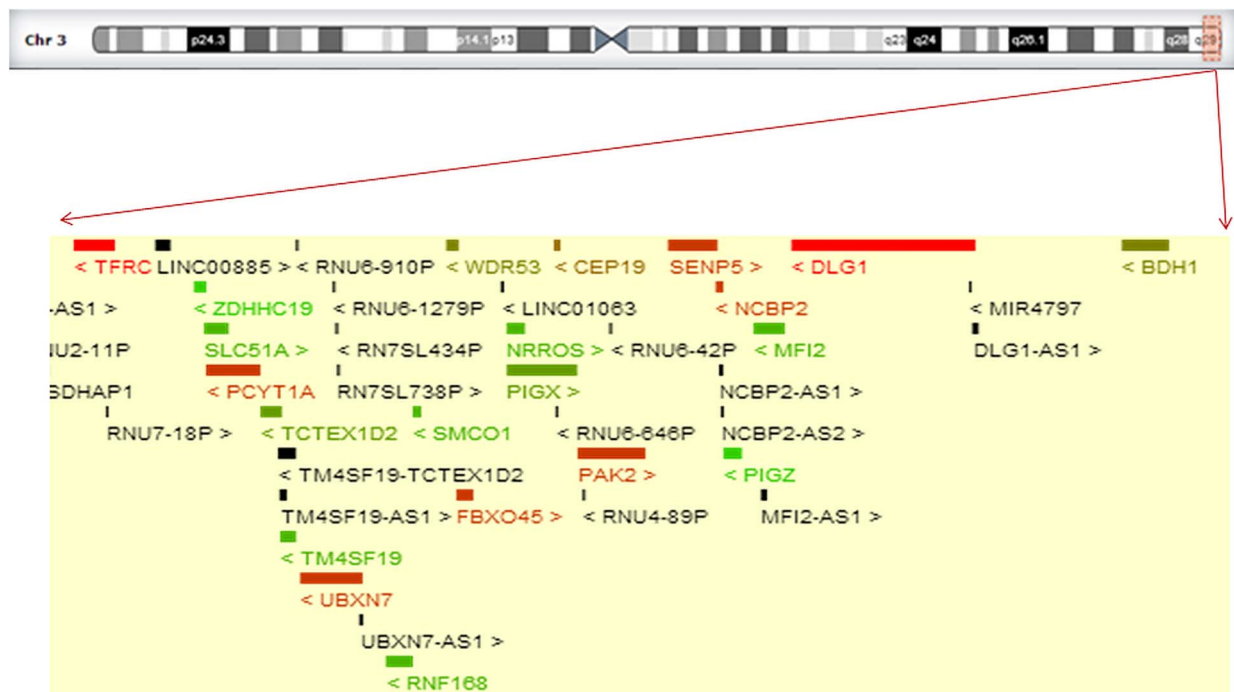


Figure 2 3q29 CNVs: recurrent 1.6 Mb deletions/duplications (chr3: 195.7–197.3 Mb). Protein-coding genes are marked in colour, the remaining are marked in black. Within protein-coding, genes have been scored according to their predicted probability of exhibiting haploinsufficiency: in red are the genes more likely to exhibit haploinsufficiency, in green the genes less likely to exhibit haploinsufficiency (adapted from Firth and colleagues¹⁶¹).

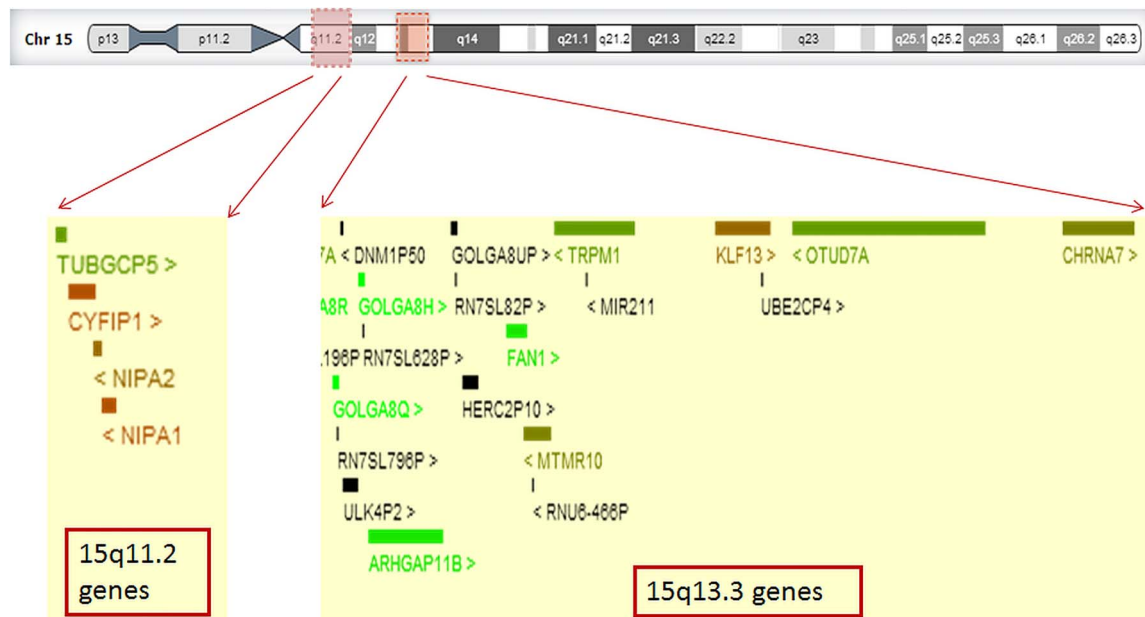


Figure 3 Chromosome 15 CNVs: recurrent 15q11.2 (break points (BP)1-BP2) deletions, ranging from 253 Kb to 1.5 Mb and encompassing the four non-imprinted genes *NIPA1*, *NIPA2*, *CYFIP1*, *TUBGCP5* and 15q13.3 (BP4-BP5) deletions/duplications (chr15: 30.91–32.44 Mb). Protein-coding genes are marked in colour, the remaining are marked in black. Within protein-coding, genes have been scored according to their predicted probability of exhibiting haploinsufficiency: in red are the genes more likely to exhibit haploinsufficiency, in green the genes less likely to exhibit haploinsufficiency (adapted from Firth and colleagues¹⁶¹).

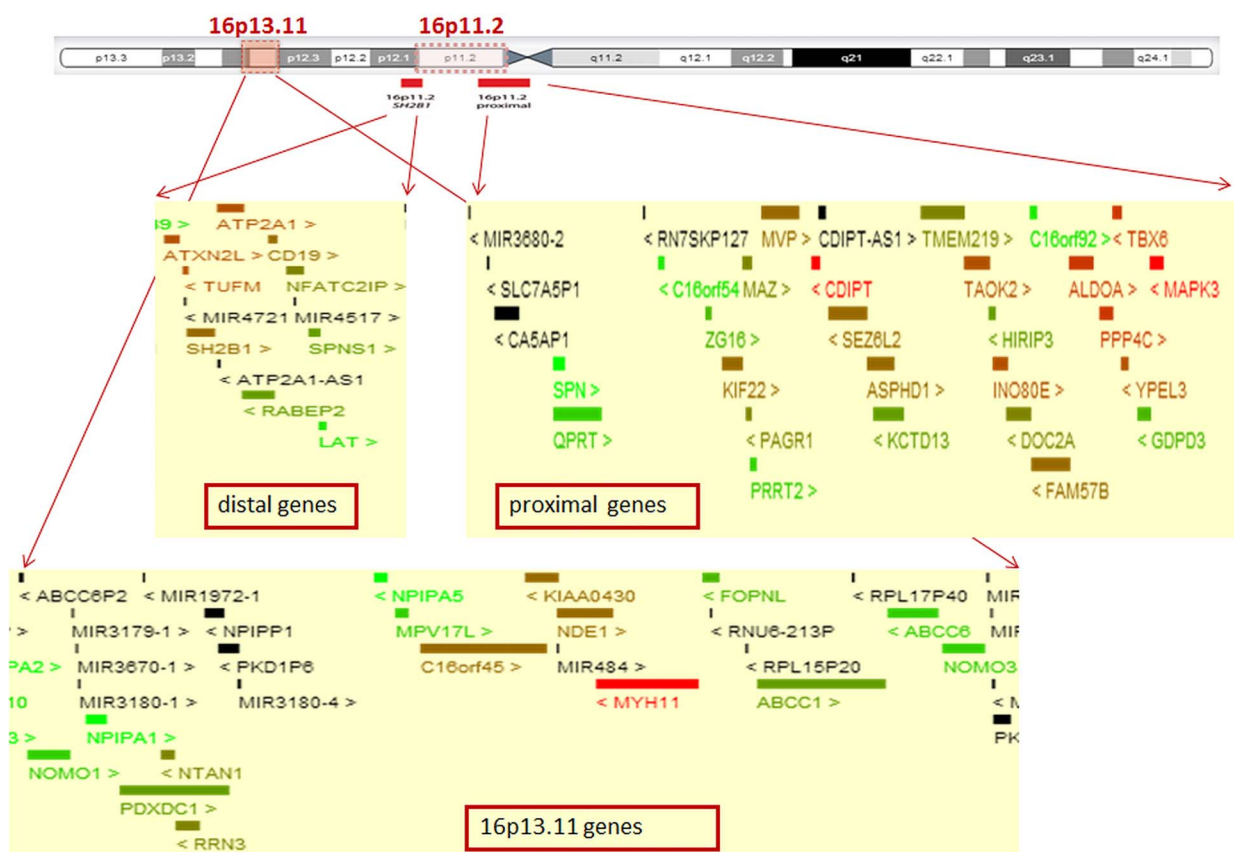


Figure 4 Chromosome 16 CNVs: recurrent 16p11.2 deletions/duplications, proximal (chr16: 29.60–30.19 Mb) and distal (chr16: 28.73–28.95 Mb); recurrent 16p13.11 deletions/duplications (chr16: 14.98–16.48 Mb). Protein-coding genes are marked in colour, the remaining are marked in black. Within protein-coding, genes have been scored according to their predicted probability of exhibiting haploinsufficiency: in red are the genes more likely to exhibit haploinsufficiency, in green the genes less likely to exhibit haploinsufficiency (adapted from Firth and colleagues¹⁶¹).

cerebral cortex of mouse models with duplication/deletion and cell lines derived from multiplex ASD families with the CNV showed that expression of all genes in the CNV region correlated well with their DNA copy number. Effects of 16p11.2 rearrangements on gene expression outside the CNV region were also observed, including apparent positional effects in *cis* and in *trans* and dysregulation of genes located in other chromosomal regions. In conclusion, alteration of 16p11.2 genes seems to disrupt expression networks that involve other genes and pathways known to contribute to ASD.⁹⁸

The 220-kb 16p11.2 distal deletion (28.73–28.95 Mb) was first described in association with severe early onset obesity alone.⁹⁹ Soon after, it was also described in patients with DD, ID and other variable phenotypical features in addition to obesity^{12 44} and, more recently, in association with SZ (table 6).^{31 43}

The minimal deleted region contains nine genes, several of which are implicated in neurological diseases (*TUFM*, *ATP2A1*), immunity and glucose homeostasis. The most likely obesity candidate gene was postulated to be *SH2B1*, involved in leptin and insulin signalling,¹⁰⁰ and implicated in the regulation of body weight and glucose homeostasis in mice.¹⁰¹

16p13.11 rearrangements

Common features of the patients with the 1.5 Mb deletions at 16p13.11 (16p13.11del) include ID, microcephaly and epilepsy, while patients carrying the reciprocal duplication have pronounced behavioural problems in addition to ID and/or CAs.^{45 102}

A threefold excess of duplications and deletions has been observed in SZ cases (table 7),^{31 46} and both rearrangements have been implicated in ADHD.^{48 103}

The 16p13.11del is significantly associated with GGE^{33 67 104} and appears to be the most prevalent single genetic risk factor

for overall seizure susceptibility (0.6% of patients with epilepsy).⁴⁷

The 16p13.11 consensus region spans seven genes (*MPV17L*, *C16orf45*, *KIAA0430*, *NDE1*, *MYH11*, *C16orf63*, *ABCC1*) (figure 4).^{48 103} Among them, the nuclear distribution gene E homologue 1 (*NDE1*) is of particular interest, because the nucleE neurodevelopment protein 1 is essential for mitosis and neurodevelopment, and interacts with the disrupted in SZ 1 protein,¹⁰⁵ implicated in SZ and in other major psychiatric disorders.^{106–108} *NDE1* deficiency impairs neurogenesis, by causing profound neuronal proliferation defects and a deficiency in cortical lamination, as observed in *Nde1*-null mice and in patients with *NDE1* homozygous mutations, who present extreme microcephaly with lissencephaly.^{106 107} Severe microcephaly, including fetal brain disruption, can also be caused by the combination of a 16p13.11del and a mutation on the non-deleted *NDE1* homologue.¹⁰⁸ As the 16p13.11 region includes other genes expressed during brain development, such as *ABCC1*, *NOMO1*, *NTAN1*, *PDXDC1*, it has been suggested that sequencing these candidate genes for second-hit mutations in patients with 16p13.11del and severe neurodevelopmental phenotypes could give new insights into these disorders.¹⁰⁸

22q11.2 rearrangements

DiGeorge syndrome, velocardiofacial syndrome or 22q11.2 deletion syndrome (22q11DS) results from 1.5–3 Mb heterozygous microdeletions on 22q11.2 locus; these deletions (22q11.2del) represent one of the most common disease-causing CNVs. The associated phenotype is variable but frequently includes cleft palate, hypocalcaemia, cardiac defects, immune dysfunction and neuropsychiatric illness.^{109–111} About 85% of patients with 22q11DS have the 3 Mb deletion (~60 genes), while the remainder have the smaller 1.5 Mb deletion (28

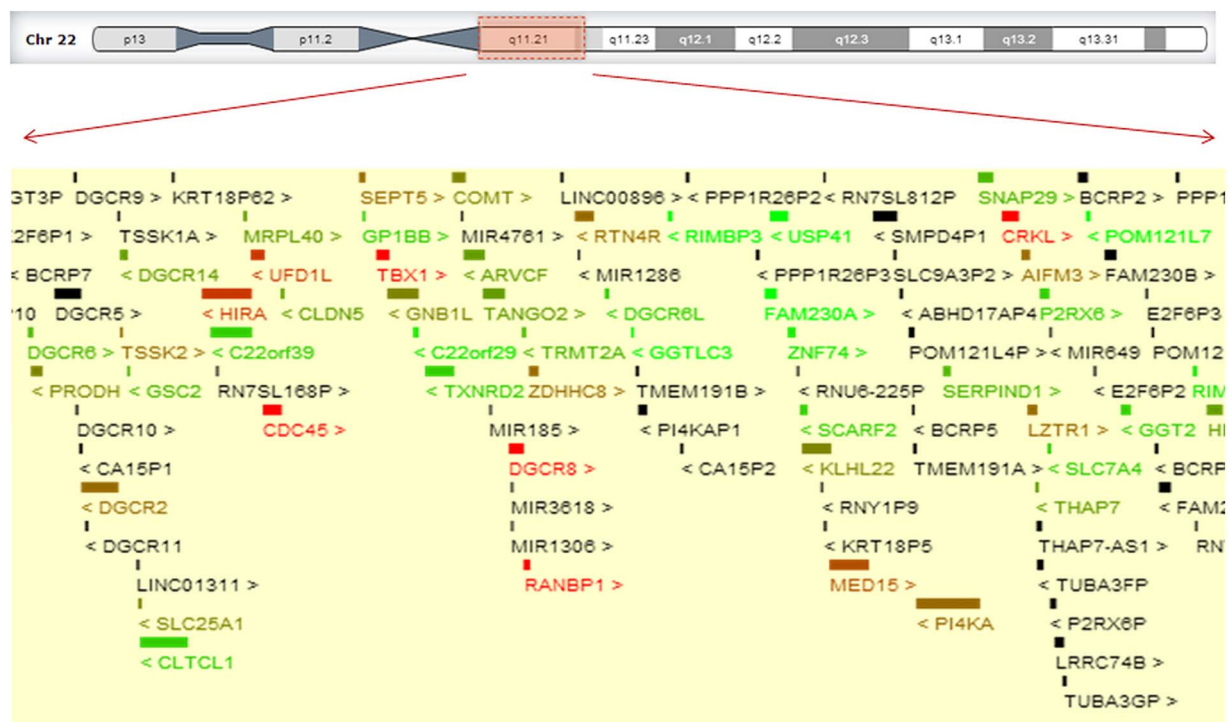


Figure 5 Recurrent 22q11.2 CNVs (chr22: 19.00–21.45 Mb). Protein-coding genes are marked in colour, the remaining are marked in black. Within protein-coding, genes have been scored according to their predicted probability of exhibiting haploinsufficiency: in red are the genes more likely to exhibit haploinsufficiency, in green the genes less likely to exhibit haploinsufficiency (adapted from Firth and colleagues¹⁶¹).

genes), or atypical deletions, containing a small number of genes (figure 5).¹¹¹

Patients with 22q11DS have variable psychiatric and cognitive presentations: children have a high prevalence of ASD, ADHD, anxiety disorders and psychotic features¹¹² while up to 30% of adolescents and adults develop SZ or affective psychosis.^{113 114} The 22q11.2del was the first CNV implicated in SZ¹¹⁵ and is now considered one of the greatest known risk factors for psychotic illness, accounting for up to 1–2% of sporadic cases of SZ (table 8).^{30 31 111 114}

The reciprocal 3 Mb duplication is usually associated with milder and more variable phenotypes: DD, speech delay and cognitive deficits have been reported in 50–80% of the patients, but asymptomatic carriers were also observed (table 7).^{42 109 116–119}

Data from genetic association studies in human patients and control subjects, indicate that a substantial number of genes are likely to contribute to 22q11DS key phenotypes.¹²⁰

The *TBX1* gene, although responsible for some major aspects of the phenotype of 22q11.2DS (abnormal facies, cardiac defects, thymic hypoplasia, velopharyngeal insufficiency of the cleft palate and parathyroid dysfunction with hypocalcaemia), does not seem to be responsible for the cognitive/neuropsychiatric features commonly seen in patients with 22q11DS.¹²¹

Two other genes within this CNV are *COMT* and *PRODH*. The *COMT* gene encodes a postsynaptic enzyme that modulates dopaminergic clearance¹²² and, given the association between dopamine deficits and several psychiatric disorders such as SZ and ADHD,¹²³ has been widely investigated. The functional polymorphism Val158Met (rs4680) affects enzyme activity and dopamine availability in brain areas where this neurotransmitter is released, such as the prefrontal cortex. The high-activity *COMT*¹⁵⁸Val allele has, therefore, been suggested as a small but reliable risk factor for SZ, at least for people of European ancestry.¹²⁴

The *PRODH* gene encodes the enzyme that converts proline to glutamate in mitochondria, dysfunction of which has been linked to the development of psychiatric illness, including SZ.¹²⁵ There is also evidence for epistatic interaction between *COMT* and *PRODH*: *Prodh*-deficient mice show *Comt* upregulation in prefrontal cortex, which likely represent a homeostatic response to enhanced dopaminergic signalling resulting from *Prodh* deficiency,¹²⁶ and elevated plasma proline levels.¹²⁷ If *COMT* upregulation is indeed one of the mechanisms used to control cortical dopaminergic hypersensitivity, then most patients with 22q11DS who are haploinsufficient for both genes, particularly those who have the low-activity *COMT*¹⁵⁸Met allele, may be at a particular disadvantage because they are unable to compensate efficiently, through *COMT*, for the cortical dopaminergic hyperactivity induced by *PRODH* deficiency.^{114 126 127}

Based on human and mouse model studies of 22q11.2 rare CNVs, Hiroi proposed that alterations of a distinct set of multiple, non-contiguous genes encoded in this chromosomal region, together with environmental factors and modulatory impacts of the genetic background, could variably shift the probabilities of phenotypes along a predetermined developmental trajectory.¹²⁸

IMPACT OF CNVS

The predictive value of genetic variants depends, in part, on their penetrance, defined as the probability of an individual with a certain genotype to present a phenotype at all, whereas

the concept of variable expressivity pertains to the variability in the spectrum of symptoms/phenotype.

Vassos and colleagues estimated the penetrance of CNVs associated with SZ, at 15q13.3, 1q21.1, 15q11.2, 17p12, 2p16.3, 16p13.1 and 16p11.2 and concluded that the highest penetrance was observed for 15q13.3del (6–9%) and the lowest for 15q11.2del (2%).¹²⁹ Calculation of the frequencies of 70 implicated CNVs in patients, controls and the general population led to the conclusion that, except for 16p11.2dup, 3q29del, 16p13.1dup and the smaller 15q13.3 (*CHRNA7*) duplications, the penetrance of CNVs is higher for the development of a disorder from the group of DD/ASD/CAs than for SZ. This observation has also strengthened the evidence of a genetic overlap, at least for some CNVs, among DD, ASD and SZ; some CNVs are so highly pathogenic and penetrant that they cause earlier-onset disorders, such as DD/ASD/CAs, precluding the diagnosis of SZ.¹³⁰

Studying the functional impact of CNVs and the neurobiology of NDs

The identification of this unexpectedly abundant type of genetic variation and the increasingly clear role of CNVs in NDs has led to the need to develop appropriate models for the study of disease pathogenesis, aiming at the development of therapeutic strategies for these diseases.

Despite the difficulty of modelling all aspects of human psychiatric and neurodevelopmental phenotypes in animals (eg, hallucinations and delusions characteristic of SZ, hard to characterise in other species), animal models may contribute to the elucidation of brain anatomy, functional connectivity, cognitive and behavioural features, and also molecular mechanisms that reflect aspects of human phenotypes.¹³¹ Among the most used are mouse models, which can be engineered in several ways: some express multiple genes within the human chromosomal region that is being studied; others have the syntenic region deleted or duplicated; finally, there are individual gene knockout or overexpression models which allow us to dissect the contribution of a particular gene to a given phenotype.^{131 132} Other models, like zebra fish or *Caenorhabditis elegans*, are also used particularly to assess the function of particular genes.^{133 134} More recently, the possibility of using human induced pluripotent stem cells (hiPSCs) has opened a wide range of experiment possibilities, including in drug screening.¹³⁵

Animal models

Animal models of CNV-related neurodevelopmental impairment are not very numerous but some interesting examples exist that illustrate the possibilities in this field.

Haploinsufficiency of *Cyfp1*, believed to be one of the key aspects of the 15q11.2 (BP1-BP2) deletions, produces fragile-X-like phenotypes in mice, which is consistent with a role for the interaction of *Cyfp1* and *Fmrp* in regulating activity-dependent translation in neurons.¹³⁶

A 15q13.3 microdeletion mouse model (Df(h15q13)/₊), generated by hemizygous deletion of the orthologous region, displays key phenotypes including SZ, epilepsy and aggression, all associated with the human syndrome.¹³⁷

Mice with deletion (as well as reciprocal duplication) of the chromosomal region corresponding to the human 16p11.2 locus, have provided functional evidence that 16p11.2-CNVs cause brain and behavioural anomalies. Notably, the macrocephaly (with deletion) and microcephaly (with duplication) observed in human subjects were replicated in mice. Regarding behaviour, 16p11.2del mice showed hyperactivity, difficulty

adapting to change, sleeping abnormalities, and repetitive or restricted behaviours, while 16p11.2dup animals were hypoactive.¹³⁸ Half of the 16p11.2del mice died postnatally, suggesting a potential link between 16p11.2-CNVs and infant mortality, that remains to be explored in humans; those that survived to adulthood were healthy and fertile, but exhibited behaviour changes characteristic of rodents with lateral hypothalamic and nigrostriatal lesions.¹³⁸

Consistently with human postmortem studies showing that neuronal migration abnormalities in the cerebral cortex are a feature of 22qDS,¹³⁹ diminished dosage of 22q11 genes disrupts neurogenesis and cortical development in mice.¹⁴⁰ The 22q11.2del disrupts an established molecular mechanism—Cxcr4-mediated signalling—that regulates cortical interneuron migration and placement.¹⁴¹ Deficits of various degrees across hippocampus and alterations in synaptic plasticity and structural connectivity within the prefrontal cortex, thought to be contributors to the 22q11.2-related cognitive and psychiatric impairments, were shown to occur in other 22q11.2del mouse models.^{142–143} Altered brain microRNAs and abnormalities in the formation of neuronal dendrites and spines, including those in corticocerebellar, corticostriatal and corticolimbic circuits were also observed in these models.^{144–145} Future studies with these mouse models should allow an increased understanding of pathogenic processes underlying NDs as well as the design and testing of suitable therapeutic strategies for these disorders.

Human induced pluripotent stem cells

hiPSCs are adult pluripotent stem cells generated from somatic cells that can be derived from adult humans, and represent a potentially limitless source of human cells to study disease: hiPSCs also make possible the study of human neurons, a previously inaccessible cell type, carrying the genetic information from patients with a specific mutation or a neuropsychiatric disease.¹⁴⁶

Patient-derived cells (eg, dermal fibroblasts from a skin biopsy or peripheral blood mononuclear cells) can be reprogrammed into iPSCs by forced expression of four pluripotency-associated transcription factors: *OCT4*, *SOX2*, *KLF4* and *c-MYC*. These cells are similar to human embryonic stem cells in morphology, proliferation, surface antigens, gene expression, epigenetic status of pluripotent cell-specific genes and telomerase activity.¹⁴⁷

Although there are no publications to date describing the CNVs described here, hiPSCs have been used to model NDs that include autistic features: neurons differentiated from hiPSCs of affected individuals or from genetically modified hiPSCs exhibited disease-related phenotypes, such as fewer synapses, smaller soma size, deficits in calcium signalling and in spontaneous excitatory synaptic communication, when compared with unaffected control neurons.¹⁴⁸ hiPSC-derived neurons in patients with SZ showed an aberrant migration, increased oxidative stress,¹⁴⁹ significantly reduced neuronal connectivity, reduced neurite outgrowth, reduced dendritic levels of PSD95 and altered gene expression profiles; interestingly, key cellular and molecular elements of the SZ phenotype were ameliorated following treatment of SZ hiPSC neurons with the antipsychotic loxapine.¹⁵⁰

The limitations of hiPSC-based approaches for studying psychiatric disease are mainly neuron-to-neuron variability, hiPSC-to-hiPSC variability and patient-to-patient variability and, therefore, hiPSC-based studies will not replace MRI, post-mortem and genetic studies of patients with psychiatric disorders.¹⁵¹ Nevertheless, the development of these models opens new avenues for the deeper understanding of pathogenic

mechanisms and—importantly—for the development of new therapeutic strategies for these disorders, by means of large-scale screening of chemical libraries with disease-specific hiPSCs.¹³⁵

TRANSLATION OF THE RECENT KNOWLEDGE TO THE CLINICAL CONTEXT—GENETIC COUNSELLING

Until recently, counselling of a patient/family with history of neuropsychiatric disease too often meant discussion of empirical risks since in the majority of cases the aetiology was not known. A good deal of the counselling session would be dedicated to clearly transmitting the value and limitations of these empirical risks and what this would translate into in the patient's and his/her relatives' life. In this context, unburdening the patient, parents and extended family from stigma and guilt was—and still is—paramount.

The technological advances in molecular genetics in the last decade—namely CMA and WES—have, however, revolutionised the field of medical genetics regarding diagnostic yield.

As a matter of fact, the 15–20% diagnostic yield of CMA led multiple medical entities (such as the American College of Medical Genetics, American Academy of Neurology and the American Academy of Pediatrics) to recommend microarray as a first-tier clinical diagnostic test for individuals with ASD, ID/DD or multiple CAs.¹⁵² This contributed to: (A) a better understanding of the entire spectrum of fully penetrant genes and regions that cause syndromic NDs, the current understanding being that the spectrum fades into non-syndromic mild ID and ASD; (B) detection of CNVs that are significantly enriched in cases but also present in controls. In fact, the highly increased risk of developing neurodevelopmental phenotypes associated with some of these CNVs makes them an unavoidable element in the clinical context in paediatrics, neurology and psychiatry and should be addressed by a multidisciplinary clinical team, ideally including a geneticist.

Both scenarios are challenging in terms of counselling. In the case of a child with a significant disability (in the context of syndromic or non-syndromic disease) due to a de novo CNV with complete penetrance, genetic counselling has straightforward medical benefits such as a tailored follow-up for the child, accurate genetic counselling for the family and the possibility of pre-natal diagnosis. Much greater challenge is faced when counselling for a recurrent CNV with known incomplete penetrance and/or variable expressivity, or when there is a degree of uncertainty on whether the CNV indeed poses risk for health: in this case, the translation of this recent knowledge into clinical practice has not been trivial. Even though it may be tempting to postpone its use in the clinical context—until more solid data or guidelines are developed—the complexity of these findings should be embraced since some of these CNVs present ORs above 5 that have been replicated in independent studies. Interestingly, risk factors for cancer development or cardiovascular disease frequently have lower multivariate-adjusted ORs and yet they are heavily used in a patient's clinical management. This is because many of these risk factors are preventable (eg, obesity) or help us set a lower threshold for screening or intervention. But the same applies for ND, where early intervention (eg, stimulation and behavioural therapy) and identification of other factors that could contribute to developmental difficulties or arrest (eg, vision and hearing screening) should be considered.

Incomplete penetrance and variable expressivity

It is known that deletions and duplications of the same *locus* can present with identical and mirror features. Also, in general,

the penetrance of deletions is higher than that of duplications. For example, 16p11.2del are more penetrant and more frequently de novo events than duplications.¹⁵³

In addition to incomplete penetrance, many CNVs also present variable expressivity. For example, the 15q13.3del may be detected in individuals who are ascertained with different NDs such as ID, SZ and BD. This may be viewed as interfamilial variability. However, this can also translate into intrafamilial variability in a scenario where, for example, a child with ASD has an apparently healthy mother and maternal relatives with SZ and BD. The recognition of the incomplete penetrance and the variable expressivity is needed in order to assemble the relevant information for counselling.

Penetrance and variable expressivity might be influenced by other genetic, epigenetic and environmental factors. Different risk elements might contribute to the preferential development of one neurophenotype over another, as well as determine severity. Different models to explain variable expressivity have been suggested: additive (two co-occurring CNVs affecting independent functional modules/pathways) and epistatic (two CNVs affecting the same functional module/pathway).¹⁵⁴ The study of more than 20 000 cases and around 14 500 controls offered evidence for the additive model in the case of 16p12.1del.¹⁵⁵

Carriers, controls and general population

Neuropsychiatric profiling of patients with 22q11.2del has shown that these patients present a wide IQ range, from normal to moderate ID (ie, $-3SD$ below the mean).¹⁵⁶ A similar study design was used to evaluate patients with 16p11.2del, which showed that individuals with the deletion had an average IQ 1 SD below the population mean). However, when compared with relatives without the deletion, individuals with the 16p11.2 deletion had a 1.8 standard deviation loss.¹⁵⁷

Two conclusions can be inferred: (1) the very same damaging CNV might impact differently in different individuals, depending on their genetic background; (2) one may be able to predict the phenotypical severity of an individual with a deleterious CNV by using parents as proxies. This knowledge could be useful in postnatal diagnosis, for tailored follow-up and early intervention, and in prenatal care.¹⁵⁸

Complementary, detailed study of carriers of neuropsychiatric CNVs revealed that they show cognitive abilities and brain structure changes situated between those of controls (ie, without a neuropsychiatric CNV) and patients with NDs, even though they often did not fulfil criteria for ASD, ID or SZ.¹⁵⁹ One could speculate that what is sometimes perceived as lack of penetrance is actually variable expressivity, which could be detectable provided more granular phenotyping had been performed.

Prenatal diagnosis

Counselling in a prenatal diagnosis setting is a particularly delicate task. This is true in the case of a de novo fully penetrant pathogenic CNV, but even more so for CNVs with incomplete penetrance and variable expressivity or for variants of uncertain significance. The latter is a rare event (about 1%)¹⁶⁰ but a source of great anxiety and request of multiple/serial complementary exams in the hope of shedding some light on the decisions need to be made within a narrow timeframe.

Parental testing can bring some solace when it is shown that the variant is inherited, or escalating of anxiety if it is shown to be de novo. And yet, inheritance of a variant from a healthy parent is no guarantee of it being benign—and the other way around. In case one of the parents is a carrier of a CNV with

Box 1 Summary points

1. CNVs contribute to a significant proportion of risk of developing a neurodevelopmental disorder (ND), and brought to the forefront the relevance of rare de novo and essentially private mutations in this group of disorders.
2. CNVs may impact dosage-sensitive gene expression in normal brain development or unmask recessive mutations in the other allele of the same gene.
3. A broad phenotypical spectrum, ranging from normal development, to cognitive impairment, is associated with these rearrangements.
4. Genetic and environmental additional events are likely necessary to push the neuropsychiatric phenotype beyond threshold of disease.
5. Counselling for a CNV poses a great challenge, due to the variability on penetrance and expressivity and to the uncertainty on whether a given CNV poses risk for health.

incomplete penetrance, additional attention should be devoted to not stigmatise the parent or distort the couple dynamics.

Rosenfeld and colleagues calculated empirical risks taking into account frequencies of 13 recurrent CNVs in cases and controls and confirmed an already known point: deletions are usually more penetrant events than the reciprocal duplications. The associated risk of an abnormal phenotype for distal 1q21.1del is ~37% versus ~29% for duplications; ~62.4% for distal 16p11.2del versus 11.2% for duplications; 46.8% for proximal 16p11.2del versus 27.2% for duplications. The risk associated with 16p13.11del is 13.1%; the risk associated with 22q11.2dup is 21.9%,³⁵ whereas the risk associated with the reciprocal deletion is ~55%, at least for SZ.¹²⁹ This is useful

Box 2 Translation into the clinical context

1. Microarrays are currently considered first-tier clinical diagnostic test for individuals with autism spectrum disorders (ASD), intellectual disability (ID)/developmental delay (DD) or multiple congenital abnormalities (CAs).
2. Risk-associated recurrent CNVs are nowadays an unavoidable element in the clinical context in paediatrics, neurology and psychiatry and should be addressed by a multidisciplinary clinical team, including a clinical geneticist.
3. The recognition of the incomplete penetrance and variable expressivity is needed in order to assemble the relevant information for counselling.
4. Penetrance and variable expressivity of CNVs might be influenced by other genetic, epigenetic and environmental factors. Taking relatives as proxies for predicting prognosis may be useful.
5. Revisiting the literature on a regular basis is mandatory in a field of exponentially growing knowledge.
6. Risk-associated CNVs in a prenatal diagnosis context should be approached cautiously with a strategy that includes parental testing and psychological profiling and takes into account family history, pregnancy history, parental resilience, capability of accepting increased risk, religious beliefs, ethical orientations and socioeconomic support network.

Box 3 Future perspectives

1. Further gene expression assays (either using lymphoblastoid cell lines or postmortem brain samples) are necessary to address the impact of CNVs in dosage-sensitive gene expression in normal brain development.
2. Functional analysis using animal models and/or human induced pluripotent stem cells (hiPSCs) are important for the deeper understanding of pathogenic mechanisms and for the development of new therapeutic strategies.
3. The complete characterisation (including genetic and environmental aspects) of: (A) large groups of patients with a given CNV and; (B) large cohorts of control individuals carrying the same CNV, will hopefully give some insights concerning the additional events necessary to push the neuropsychiatric phenotype beyond threshold of disease.
4. As the Encyclopedia of DNA Elements (ENCODE) project moves forward, different genome elements, including 'non-coding' sections of the genome, will be better defined, characterised and integrated in order to assess their roles in human biology and disease.

information as a ~10% risk of neurodevelopmental problems associated with a 15q11.2 deletion is more reassuring than the ~50% risk associated with a 16p11.2 proximal deletion.³⁵

Still, these numbers should be approached cautiously and take into account family history, pregnancy history, parental resilience, capability of accepting increased risk, religious beliefs, ethical orientations and socioeconomical network of support (boxes 1–3).

Care should be taken to avoid psychological harm to carriers (feelings of blame and low self-esteem) and their families (discrimination of an entire branch or community). Multiple counselling sessions with several relatives are needed to evaluate who is at risk and to reinforce the meaning of arid statistical concepts. When emotional stress overpowers reasoning, psychotherapeutic follow-up may be beneficial.

Correction notice This article has been corrected since it published Online First. The first paragraph has been corrected under the 'Carriers, controls and general population' heading.

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